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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,689	12/17/2004	Antonio Guarna	50294/014001	5376

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EXAMINER	
CAPPS, KEVIN J	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/518,689	GUARNA ET AL.	
	Examiner	Art Unit	
	Kevin J. Capps	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-42* is/are pending in the application.

4a) Of the above claim(s) *27-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-26,41 and 42* is/are rejected.

7)☒ Claim(s) *25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 22-42 are pending. Claims 22-26, 41, and 42, drawn to compounds of general formula (I) and pharmaceutical compositions comprising said compounds, are examined on the merits herein.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 22-26, 41, and 42, drawn to compounds of general formula (I) and pharmaceutical compositions comprising said compounds, in the reply filed on May 30, 2006, is acknowledged. The traversal is on the ground(s) that Applicant's suggestion to use compounds having the 3-aza-bicyclo[3.2.1]octane core in pharmaceutical practice constitutes a special technical feature and unity of invention therefore exists in the instant application. This argument is not found persuasive because compounds having the 3-aza-bicyclo[3.2.1]octane core have been described in the art and their use in pharmaceutical practice has been suggested. First, Applicant's submission that PCT Unity of Invention standards for restriction should apply to the instant application filed under 35 USC § 371 is acknowledged. It is noted that PCT Unity of Invention standards were the basis of the restriction requirement.

3. Regarding Applicant's argument that the use of compounds having the 3-aza-bicyclo[3.2.1]octane core in pharmaceutical practice constitutes a special technical

feature, the Examiner points to the first page of Guarna et al. (Guarna et al. *J. Org. Chem.* **1999**, *64*, 7347-7364.), which states, "Peptide isosteres are compounds that can replace one or more amino acids in a bioactive peptide leading to modified structures possibly displaying more favorable pharmacological properties than the prototype. In several cases, the modified peptide shows a higher metabolic stability, better bioavailability, and higher receptor affinity or selectivity." (emphases added). Guarna et al. go on to discuss five properties of peptide isosteres that would achieve these desired pharmacological properties. Guarna et al. state, "We have envisioned that some of...these features could be found in the bicyclic structure based upon 3-aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acid skeleton". Thus, Guarna et al. suggest the pharmaceutical utility of compounds comprising the 3-aza-bicyclo[3.2.1]octane core and no special technical feature exists in the instant application.

4. Applicants further argue that PCT Administrative Instructions, Annex B, Part 1(e), dictates that different categories of inventions can be included in the same application provided that the contribution over the prior art of the products corresponds to the contribution of the methods of use over the prior art. For the reason discussed above, the instantly claimed products have no special technical feature that defines a contribution over the prior art. Thus, the methods of using the products cannot have a special technical feature that corresponds to that of the products. Thus, Unity of Invention does not exist in the instant application and restriction is proper.

The requirement is still deemed proper and is therefore made FINAL.

5. Claims 27-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 30, 2006.

Priority

6. Applicant's claim of priority to Italian Patent Application FI2002A000107, filed June 19, 2002, is acknowledged.

Information Disclosure Statement

7. The information disclosure statement (IDS) filed on December 17, 2004, is in compliance with the provisions of 37 CFR 1.97. Accordingly, the IDS is being considered by the Examiner.

Claim Objections

8. Claim 25 is objected to because of the following informalities: The substituent R_6 for compound 127 should be --*(S)*-COOH--. Also, for the sake of consistency, it is requested that the R_6 substituent entries be written in the same format (compare compounds 110-125 with compounds 126-135). It is also requested that at pp. 6 and 11 of the claims, the table be reformatted so that the columns are aligned and it is easier to read the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claim 41 is rejected under 35 U.S.C. 102(b) as being anticipated by Van Cauwenberghe et al. (Van Cauwenberghe et al. *Heterocycles* **1975**, *3*, 101-107.).

11. Van Cauwenberghe et al. teach the compound of formula (I) wherein X is H, Y and Z are O, R_1 is C_1 alkyl, R_2, R_3, R_4, and R_5 are H, and R_6 is CH_2NRR', wherein R and R' are C_1 alkyl (see compound III on p. 106). Thus, Van Cauwenberghe et al. anticipate the instantly claimed invention.

12. Claim 41 is rejected under 35 U.S.C. 102(b) as being anticipated by May et al. (Applicant-cited reference on IDS: May et al. *J. Pharmaceutical Sciences* **1968**, *57*, 511-513.).

13. May et al. teach the compound of formula (I) wherein X is H, Y and Z are O, R_1, R_2, R_4, R_5, and R_6 are H, and R_3 is C_1 alkyl (see *N*-methyl-6,8-dioxa-3-azabicyclo[3.2.1]-octane on p. 512, col. 1). Thus, May et al. anticipate the instantly claimed invention.

14. Claim 41 is rejected under 35 U.S.C. 102(b) as being anticipated by Guidi et al. (Guidi et al. *Arch. Pharm. Pharm. Med. Chem.* **1997**, *330*, 201-202.).

15. Guidi et al. teach the compound of formula (I) wherein X, Y, and Z are O, R_1, R_4, and R_5 are H, R_2 and R_3 are aryl C_1 alkyl, and R_6 is C(O)OR, wherein R is C_1 alkyl (see compound 3 on p. 201). Thus, Guidi et al. anticipate the instantly claimed invention.

16. Claim 41 is rejected under 35 U.S.C. 102(b) as being anticipated by Wang et al. (Wang et al. *J. Chem. Soc., Perkin Trans. 1*, **1996**, *1*, 209-212.).

17. Wang et al. teach the compound of formula (I) wherein X, Y, and Z are O, R_2, R_4, and R_5 are H, R_1 and R_6 are aryl, and R_3 is C_1 alkyl (see compound 12 on p. 210). Thus, Wang et al. anticipate the instantly claimed invention.

18. Claims 22-24, 26, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Guerret et al. (US 4,463,004).

19. Guerret et al. teach compounds within the scope of the instant formula (I) wherein X is H, Y and Z are O, R_2, R_4, R_5, and R_6 are H, R_1 is H, alkyl having at least 4 carbons, cyclohexyl, or aryl, and R_3 is C_1 to C_4 alkyl, cyclohexyl, or benzyl (claim 1; Table I). Many compounds within the scope of the instant formula (I) are exemplified (see compounds 18, 37, and 43 in Table I, for example). Guerret et al. teach that the compounds have "pharmacological properties", particularly "analgesic activity" (col. 17, lines 12-56). Guerret et al. teach preparation of the compounds as pharmaceutical compositions for administration as analgesics (col. 17, line 57-col. 18, line 15). Thus, Guerret et al. anticipate the instantly claimed inventions.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

22. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Van Cauwenberghe et al. (Van Cauwenberghe et al. *Heterocycles* **1975**, *3*, 101-107.).

23. Van Cauwenberghe et al. teach the compound of formula (I) wherein X is H, Y and Z are O, R_1 is C_1 alkyl, R_2, R_3, R_4, and R_5 are H, and R_6 is CH_2NRR', wherein R and R' are C_1 alkyl, as discussed above (see compound III on p. 106).

24. Van Cauwenberghe et al. do not teach compounds of formula (I) wherein X is H, Y and Z are O, R_1 is C_1 alkyl, R_2, R_3, R_4, and R_5 are H, and R_6 is CH_2NRR', wherein R_1, R, or R' are greater than C_1 alkyl.

25. Adjacent homologs are considered to be obvious absent unexpected results (*In re Henze*, 85 USPQ 261, 263 CCPA 1950) and members of a homologous series must possess unexpected properties not possessed by the homologous compounds

disclosed by the prior art. *In re Hass*, 141 F.2d 127, 60 USPQ 548 CCPA 1944. Thus, the person of ordinary skill in the art would have been motivated to make the compounds of Van Cauwenberghe et al. wherein X is H, Y and Z are O, R_1 is C_1 alkyl, R_2, R_3, R_4, and R_5 are H, and R_6 is CH_2NRR', wherein R_1, R, or R' are greater than C_1 alkyl with a reasonable expectation of success because they are adjacent homologs of the compounds disclosed by Van Cauwenberghe et al.

26. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over May et al. (Applicant-cited reference on IDS: May et al. *J. Pharmaceutical Sciences* **1968**, *57*, 511-513.).

27. May et al. teach the compound of formula (I) wherein X is H, Y and Z are O, R_1, R_2, R_4, R_5, and R_6 are H, and R_3 is C_1 alkyl (see *N*-methyl-6,8-dioxa-3-azabicyclo[3.2.1]-octane on p. 512, col. 1).

28. May et al. do not teach the compound of formula (I) wherein X is H, Y and Z are O, R_1, R_2, R_4, R_5, and R_6 are H, and R_3 is greater than C_1 alkyl.

29. For the reasons discussed above, the person of ordinary skill in the art would have been motivated to make the compounds of May et al. wherein R_3 is greater than C_1 alkyl with a reasonable expectation of success because adjacent homologs are prima facie obvious absent unexpected results.

30. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guidi et al. (Guidi et al. *Arch. Pharm. Pharm. Med. Chem.* **1997**, *330*, 201-202.).

31. Guidi et al. teach the compound of formula (I) wherein X, Y, and Z are O, R_1, R_4, and R_5 are H, R_2 and R_3 are aryl C_1 alkyl, and R_6 is C(O)OR, wherein R is C_1 alkyl (see compound 3 on p. 201).

32. Guidi et al. do not teach compounds of formula (I) wherein X, Y, and Z are O, R_1, R_4, and R_5 are H, R_2 and R_3 are aryl alkyl with alkyl greater than C_1, and R_6 is C(O)OR, wherein R is greater than C_1 alkyl.

33. For the reasons discussed above, the person of ordinary skill in the art would have been motivated to make the compounds of Guidi et al. wherein R_2 and R_3 are aryl alkyl with alkyl greater than C_1, and R_6 is C(O)OR, wherein R is greater than C_1 alkyl with a reasonable expectation of success because adjacent homologs are prima facie obvious absent unexpected results.

34. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Wang et al. *J. Chem. Soc., Perkin Trans. 1*, **1996**, *1*, 209-212.).

35. Wang et al. teach the compound of formula (I) wherein X, Y, and Z are O, R_2, R_4, and R_5 are H, R_1 and R_6 are aryl, and R_3 is C_1 alkyl (see compound 12 on p. 210).

36. Wang et al. do not teach compounds of formula (I) wherein X, Y, and Z are O, R_2, R_4, and R_5 are H, R_1 and R_6 are aryl, and R_3 is greater than C_1 alkyl.

37. For the reasons discussed above, the person of ordinary skill in the art would have been motivated to make the compounds of Wang et al. wherein R_2 and R_3 are aryl alkyl with alkyl greater than C_1, and R_6 is C(O)OR, wherein R_3 is greater than C_1 alkyl

with a reasonable expectation of success because adjacent homologs are prima facie obvious absent unexpected results.

38. Claims 22-24, 26, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guerret et al. (US 4,463,004).

39. Guerret et al. teach compounds of the instant formula (I) wherein X is H, Y and Z are O, R_2, R_4, R_5, and R_6 are H, R_1 is H, alkyl having at least 4 carbons, cyclohexyl, or aryl, R_3 is C_1 to C_4 alkyl, cyclohexyl, or benzyl (claim 1; Table I). Guerret et al. teach that the compounds have "pharmacological properties", particularly "analgesic activity" (col. 17, lines 12-56). Guerret et al. teach preparation of the compounds as pharmaceutical compositions for administration as analgesics (col. 17, line 57-col. 18, line 15).

40. Guerret et al. do not teach compounds of the instant formula (I) wherein X is H, Y and Z are O, R_2, R_4, R_5, and R_6 are H, R_1 is alkyl having less than 4 carbons, and R_3 is greater than C_4 alkyl.

41. For the reasons discussed above, the person of ordinary skill in the art would have been motivated to make the compounds of Guerret et al. wherein R_1 is alkyl having less than 4 carbons or R_3 is greater than C_4 alkyl with a reasonable expectation of success because adjacent homologs are prima facie obvious absent unexpected results.

42. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (WO 01/64686).

43. Guarna et al. teach the instant compounds 138 and 142 with undefined stereochemistry (see compound 214 on p. 43).

44. Guarna et al. do not teach the resolved stereoisomers of compound 214, i.e., the instantly claimed compounds 138 and 142.

45. The expectation with regard to stereoisomers is that activities as they pertain to living systems are expected to be different. *In re Adamson*, 275 F.2d 952, 125 USPQ 233 (CCPA 1960). The fundamentals of optical activity and stereoisomerism are well known to persons having ordinary skill in the art. A person having ordinary skill in the art would have known how to resolve the racemic mixture and would have been motivated to do so with the reasonable expectation of achieving stereoisomers having substantially different pharmacological activity. Thus, the instantly claimed stereoisomers of compound 214 in Guarna et al. would have been obvious to the person of ordinary skill in the art at the time of invention.

46. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being obvious over Guarna et al. (US 2003/0176414).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject

matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2). This US application is the national stage entry of the international application published as WO 01/64686. Therefore, the basis of this rejection is the same as that stated above.

47. Claims 22-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (WO 01/64686).

48. Guarna et al. teach the instant compounds 138 and 142 with undefined stereochemistry (see compound 214 on p. 43). As discussed above, the instantly claimed resolved stereoisomers of the compounds of Guarna et al. would have been obvious to the ordinary skilled artisan. Guarna et al. also teach that their compounds are used to "discover new leads for therapeutical applications." (p. 3, lines 9-11).

49. It would have been obvious to the person of ordinary skill in the art to formulate the compounds of Guarna et al. with pharmaceutically acceptable excipients as a pharmaceutical composition to arrive at the instantly claimed invention.

50. The person of ordinary skill in the art would have been motivated to formulate the compounds of Guarna et al. with pharmaceutically acceptable excipients as a pharmaceutical composition because Guarna et al. teach that the compounds are intended for therapeutic applications. The person of ordinary skill in the art would have expected that the compounds could be formulated with routinely used, pharmaceutically acceptable excipients absent evidence to the contrary.

51. Claims 22-26 are rejected under 35 U.S.C. 103(a) as being obvious over Guarna et al. (US 2003/0176414).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under

35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2). This US application is the national stage entry of the international application published as WO 01/64686. Therefore, the basis of this rejection is the same as that stated above.

52. Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (Guarna et al. *Tetrahedron: Asymmetry* **2000**, *11*, 4227-4238.).

53. Guarna et al. teach the instant compounds 34, 58, and 176, as defined in claim 25 (see compounds 11-13 on p. 4230).

54. Guarna et al. do not teach the instant compounds 35, 59, or 177, as defined in claim 25, which are stereoisomers of the above-cited compounds.

55. The expectation with regard to stereoisomers is that activities as they pertain to living systems are expected to be different. *In re Adamson*, 275 F.2d 952, 125 USPQ 233 (CCPA 1960). The fundamentals of optical activity and stereoisomerism are well known to persons having ordinary skill in the art. A person having ordinary skill in the art would have known how to make the individual stereoisomers, and would have been motivated to do so with the reasonable expectation of achieving stereoisomers having substantially different pharmacological activity. Thus, the instantly claimed stereoisomers of compounds 11-13 in Guarna et al. would have been obvious to the person of ordinary skill in the art at the time of invention because the compounds contain the same atomic connectivity and differ in only one stereocenter and, as stated, it is well known in the art how to make or resolve stereoisomers through routine experimentation.

56. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scarpi et al. (Scarpi et al. *Bioorg. Med. Chem.* **2001**, *9*, 1625-1632.).

57. Scarpi et al. teach the instant compound 32, as defined in claim 25 (see compound 1 on p. 1627).

58. Scarpi et al. do not teach the instant compound 33, as defined in claim 25, which is a stereoisomer of the instant compound 32.

59. The expectation with regard to enantiomers is that activities as they pertain to living systems are expected to be different. *In re Adamson*, 275 F.2d 952, 125 USPQ 233 (CCPA 1960). The fundamentals of optical activity and stereoisomerism are well known to persons having ordinary skill in the art. A person having ordinary skill in the art would have known how to make the individual enantiomers, and would have been motivated to do so with the reasonable expectation of achieving enantiomers having substantially different pharmacological activity. Thus, the instantly claimed enantiomer of compound 1 in Scarpi et al. would have been obvious to the person of ordinary skill in the art at the time of invention because it contains the same atomic connectivity as the compound 1 of Scarpi et al. and would require only routine experimentation to prepare.

60. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Machetti et al. (Applicant-cited reference on IDS: Machetti et al. *Org. Lett.* **2000**, *2*, 3987-3990.).

61. Machetti et al. teach the instant compound 36, as defined in claim 25 (see compound 1 on p. 1627).

62. Machetti et al. do not teach the instant compound 37, as defined in claim 25, which is a stereoisomer of the instant compound 36.

63. As discussed above, resolved or pure stereoisomers of compounds known in the art as either racemates or isolated alternative stereoisomers are prima facie obvious absent a showing of unexpected results because the compounds contain the same atomic connectivity and require only routine techniques to prepare. The person of ordinary skill in the art would have been motivated to prepare the individual stereoisomers of known compounds because the principles of stereoisomerism are well-known and there is an expectation that the different stereoisomers will have different pharmacological properties.

64. Claims 22-26, 41, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guarna et al. (Applicant-cited reference on IDS: Guarna et al. *J. Org. Chem.* **1999**, *64*, 7347-7364.).

65. Guarna et al. teach compounds within the scope of the instant genus of compounds comprising the 3-aza-bicyclo[3.2.1]octane core, as well as specific compounds defined in the instant claim 25. For example, Guarna et al. teach compound 192 of the instant claim 25, which is the compound of the instant formula (I) wherein X, Y, and Z are O, R_1, R_4, and R_5 are H, R_2 is (S)-Me (C_1 alkyl), R_3 is C_1 arylalkyl, and R_6 is (R)-C(O)OR, wherein R is C_1 alkyl (see compound 12 on p. 7353). Guarna et al. teach a

general strategy for preparing all of the individual stereoisomers of the compounds comprising the 3-aza-bicyclo[3.2.1]octane core (see Chart 1 on p. 7349). As discussed above in the "Election/Restrictions" section, Guarna et al. suggest the pharmaceutical utility of the instantly claimed compounds comprising the 3-aza-bicyclo[3.2.1]octane core.

66. Guarna et al. do not explicitly teach the instant compounds 193-195 as defined in claim 25, which are stereoisomers of compound 192 of the instant claim 25. Guarna et al. do not teach compounds of formula (I) wherein X, Y, and Z are O, R_1, R_4, and R_5 are H, and wherein R_2 is alkyl greater than C_1, or R_3 is aryl alkyl with alkyl greater than C_1, or R_6 is C(O)OR, wherein R is greater than C_1 alkyl. Guarna et al. do not teach preparation of pharmaceutical compositions comprising the herein-claimed compounds comprising the 3-aza-bicyclo[3.2.1]octane core.

67. For the reasons discussed above, the herein-claimed stereoisomers of the compounds disclosed by Guarna et al. are prima facie obvious absent a showing of unexpected results, particularly considering that Guarna et al. teach a general strategy for preparing all of the possible stereoisomers. For the reasons discussed above, the herein-claimed adjacent homologs and homologous series are prima facie obvious absent a showing of unexpected results. Because Guarna et al. suggest the pharmaceutical utility of the herein-claimed compounds comprising the 3-aza-bicyclo[3.2.1]octane core, it would have been obvious to the person of ordinary skill in the art to formulate the compounds with pharmaceutically acceptable excipients to arrive at the instantly claimed inventions.

68. The person of ordinary skill in the art would have been motivated to formulate the compounds of Guarna et al. with pharmaceutically acceptable excipients as a pharmaceutical composition because Guarna et al. teach that the compounds have pharmaceutical utility, and bioactive compounds are routinely formulated as pharmaceutical compositions for administration in therapeutic methods. The person of ordinary skill in the art would have expected that the compounds could be formulated with routinely used, pharmaceutically acceptable excipients absent evidence to the contrary.

Double Patenting

69. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

70. Claims 22-26, 41, and 42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of copending Application No. 10/220,556. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds of '556 either overlap in scope or are within the scope of the instantly claimed compounds. Further, the instantly claimed pharmaceutical compositions are obvious in view of '556. The Patent Application Publication for this application (US 2003/0176414) was the basis of the 35 USC § 103 rejections set forth above. Therefore, the reasoning for this rejection is the same as that set forth above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

71. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin J. Capps whose telephone number is (571) 272-8646. The examiner can normally be reached on Monday-Friday, 7:30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KC

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER